REMARKS

Objection to Claim 126

Claim 126 is allegedly improper because it does not use proper Markush language. Claim 126 is not intended to be a Markush claim. It is a simple claim requiring multiple elements. Thus the claim uses the structure: a, b, c, and d. Claim 115 similarly uses this structure. Neither is intended to be a Markush claim.

The Rejection of Claims 26, 38, 115, 122, 123, and 126 Under 35 U.S.C. § 112, second paragraph

Claims 26, 38, 115, 122, 123, and 126 stand rejected as indefinite. The recitation of a first polypetide is said to be unclear because the claims allegedly do not recite a second polypeptide. In fact, the claims do recite a second polypeptide. Each of claims 124 and 125 recite a second polypetide. These claims depend on claims 122 and 123, respectively, which depend on claims 26 and 38, respectively. Thus, at least with regard to claims 26, 38, 122, and 123, the meaning of a first and a second polypeptide should be clear.

Claims 115 and 126 similarly refer to the same element using the same terminology ("first polypeptide"). If the use of parallel claim terms is not deemed sufficiently clear within the claim set as a whole which uses the first and second polypeptide terminology, then applicants stand ready to amend claims 115 and 126 to delete the word "first."

We request withdrawal of this rejection.

The Rejection of Claims 26, 38, 115, and 122-126 Under 35 U.S.C. § 112, first paragraph

Claims 26, 38, 115, and 122-126 stand rejected as containing new matter in violation of § 112, first paragraph. The recitations of "first" and "second" polypeptides and of a "fusion protein" allegedly violate the prohibition against addition of new matter.

Applicants had pointed to paragraph 44 of the specification as providing support. The U.S. Patent and Trademark Office asserts that it does not provide support for a first and second polypeptide that are fused to each other. In order to aid consideration, applicants provide the entire text of paragraph 44:

> **[44]** Polypeptides for immunization to raise a cytolytic T cell response are optionally from 8 to 25 amino acid residues in length. Although nonamers are specifically disclosed herein, any 8 contiguous amino acids of the nonamers can be used as well. The polypeptides can be fused to other such epitopic polypeptides, or they can be fused to carriers, such as B-7, interleukin-2, or interferon-γ. The fusion polypeptide can be made by recombinant production or by chemical linkage, *e.g.,* using heterobifunctional linking reagents. Mixtures of polypeptides can be used. These can be mixtures of epitopes for a single allelic type of an MHC molecule, or mixtures of epitopes for a variety of allelic types. The polypeptides can also contain a repeated series of an epitope sequence or different epitope sequences in a series.

The underlined sections of paragraph 44 indicate that indeed fusion polypeptides were contemplated and disclosed by applicants. The precise use of "a first" and "a second" were not disclosed, but there is no legal requirement for a claim to be supported *in ipsis verbis*. The use of such terminology in claims is conventional.

The subject matter of the claims is well supported and does not constitute new matter. Please withdraw this rejection.

The Rejection of Claim 26, 38, 115 and 126 Under 35 U.S.C. §103(a)

The U.S. Patent and Trademark Office rejects claims 26, 38, 115, and 126 as obvious over Weiskirch, in view of Argani and Quan. This rejection is respectfully traversed.

Weiskirch is cited by the patent office as teaching the delivery of a *Listeria monocytogenes* construct that expressed full-length or truncated nucleoprotein of influenza virus. Weiskirch is further cited as teaching that an MHC class I response to the influenza virus was induced in mice.

Argani is cited by the patent office as teaching that mesothelin is expressed in a variety of cancers types.

Quan is cited by the patent office as teaching that surgical excision is traditional for solid tumors, but that other therapeutic modalities are included in the standard of care.

Applicants have presented unexpected and remarkable results in its application. In response, the U.S. Patent and Trademark Office asserts that the claimed methods would have been obvious to try. Obvious to try is not, however, the correct legal standard. Something must be obvious to try with a reasonable expectation of success. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.,* 550 U.S. 398 (2007). The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). There would have been no reasonable expectation of success for the present methods. As shown in the Declaration under Rule 132, well known proteins that are involved in cancer and are over-expressed do not turn out to be successful vaccines. See Declaration at paragraph 7. Moreover, those of skill in the art would have expected that the phenomenon of immune tolerance to self antigens would prevent the successful use of mesothelin as a vaccine. See Declaration at paragraph 13.

The U.S. Patent and Trademark Office finds the Declaration unpersuasive, however. The U.S. Patent and Trademark Office states that the Declaration is trying to demonstrate unexpected results ("the declaration appears to be attempting to assert unexpected results"). This misapprehends its purpose. The Declaration demonstrates other points, because the application itself provided the unexpected results. The Declaration demonstrates that Argani's showing of over-expression of mesothelin would not have been sufficient to provide a reasonable expectation of

success for at least two reasons. First, other proteins which are similarly over-expressed do not generate an immune response. Second, the art's awareness of the natural process of immune tolerance to self antigens would have prevented one of skill in the art from having an expectation of success.

Since the Declaration was not trying to show unexpected results but rather was attempting to define the state of the art and what persons of ordinary skill in the art would understand, its discussion of other tumor antigens was pertinent and relevant. These other tumor antigens form the basis of what those of skill in the art would reasonably have expected. The dismissal of the Declaration evidence because it dealt with other tumor antigens was legal error.

The U.S. Patent and Trademark Office also dismisses the Declaration because it does not provide evidence teaching away from the invention ("there is no evidence in applicant's declaration or in the references…to suggest that one of ordinary skill in the art should not have used mesothelin epitopes to induce a T cell response to a tumor.") The U.S. Patent and Trademark Office cites *In re Rinehart* as holding that evidence showing that there was no reasonable expectation of success may support a conclusion of nonobviousness. In fact, such evidence was provided in the Declaration. Those of skill in the art would have expected a host animal to be tolerant of a self antigen, and thus would not have expected mesothelin, a self antigen, to successfully induce an immune response. See Paragraph 13. Reconsideration of the Declaration evidence is requested.

The U.S. Patent and Trademark Office dismisses the applicant's reliance on the delayed type hypersensitivity (DTH) data because the claims do not recite DTH. DTH, however, is an indicator of an immune response in the patient. It is a type of immune response. It shows that the animal/human responded to the antigen. It shows that tolerance was overcome. In fact, the claims do recite induction of a T cell response to mesothelin. DTH is one such response. Thus the discussion of DTH is directly relevant to the claimed subject matter.

The U.S. Patent and Trademark Office quotes Argani as teaching that mesothelin "has been used as a target for immunotherapy." (Office action at page 7, lines 15-16). This statement, while accurately quoted, is misleading. Argani made this statement at page 3862, column 2, lines 12-16 of

the introduction, citing references 5 and 6. Argani expands on the statement in the discussion, stating, "As a cell surface protein, mesothelin is an effective target for immuno-toxins used to treat ovarian carcinomas and malignant mesotheliomas. Thus, antibody-based immunotherapy against mesothelin may hold promise as a normal therapy for pancreatic carcinoma (5, 6)." Page 3867, column 2, lines 9-14. References 5 and 6, upon which Argani bases his statement, both teach administration of an anti-mesothelin antibody linked to a cytotoxin.[1] Thus, when Argani teaches a target for immunotherapy he refers to a target for an antibody. Antibodies are passive immunotherapy agents that do not involve inducing a T-cell response and do not require overcoming or breaking immune tolerance. Thus, Argani does not teach or suggest that mesothelin could be used as a vaccine, which requires induction of a T-cell response and breaking immune tolerance. Thus Argani does not provide a reasonable expectation of success for the claimed methods.

The U.S. Patent and Trademark Office dismisses applicants' assertion, supported by the Declaration, that one of ordinary skill in the art would have expected that immune tolerance would prevent the induction of an immune response to mesothelin. The knowledge of the phenomenon of immune tolerance to a self-antigen would have prevented the skilled artisan from having a reasonable expectation of success. The basis for the U.S. Patent and Trademarks Offices' dismissal is that "since the instant binding epitope would be expressed by a bacterial cell (the instant method administers a *Listeria monocytogenes* bacterium), one of ordinary skill in the art would presume that the MHC cells would not recognize the peptide as a self-peptide (thus having immune tolerance) because the peptide was introduced from a bacterial cell." Office Action at page 6, line 1-5.

The United States Patent and Trademark Office provides no factual support for its assertion that human peptides presented by bacterial cells are not recognized by humans as "self." If this

[1]Chowdhury et al., "Isolation of a high-affinity stable single-chain Fv specific for mesothelin from DNA-immunized mice by phage display and construction of a recombinant immunotoxin with anti-tumor activity." *Proc. Natl. Acad. Sci. USA, 95:* 669-674, 1998; and Hassan, et al., "Anti-tumor activity of K1-LysPE38QQR, an immunotoxin targeting mesothelin, a cell-surface antigen overexpressed in ovarian cancer and malignant mesothelioma," *J. Immunother., 23:* 473-479, 2000.

assertion is based on personal knowledge of the examiner, applicants request an affidavit, so that it can be subject to contradiction or explanation. 37 CFR § 1.104(d)(2). Applicants understand that merely presenting a self-antigen in a bacterial cell is not sufficient to overcome immune tolerance.

Conclusion

Claims 26, 38, 115, and 122-126 have been examined. Only claims 26, 38, 115, and 126 are rejected as obvious. Thus claims 122-125, although not so designated, are free of the prior art. Claims 122-125 were rejected as either unclear or unsupported, but applicant believes that its remarks have obviated these rejections. Thus, applicants expect that, at the very least, claims 122-125 will be designated as allowable.

Applicant believes that its remarks and declaration have also shown that under the appropriate legal standards, claims 26, 38, 115, and 126 would not be considered obvious. Should the examiner not agree, these issues stand ready for appeal.

Respectfully submitted,

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